In re of Appln. No. 09/297,668

REMARKS

Claims 144-182 presently appear in this case. Claims 157, 158, 171-176, 178 and 180-182 have been withdrawn from consideration. No claim has been allowed. The official action of October 16, 2002, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for identifying continuous peptides which simulate a discontinuous epitope of a single biological unit, i.e., which interact with a ligand which interacts with a discontinuous epitope of a single biological unit. The single biological unit may be a protein or a complex of proteins. It may also be a DNA or RNA unit. The DNA, which may be the DNA that comprises the biological unit or that corresponds to the RNA of the biological unit or that encodes the amino acid sequence of a proteinaceous biological unit, is divided into DNA fragments. A library of oligonucleotides, each comprising at least two of such fragments that are randomly ligated, is then created. Preferably, this library will contain oligonucleotides of fragment pairs in which each fragment is linked to each other fragment. If the biological unit is a protein or a complex of proteins, the oligonucleotides are inserted into an expression system and then expressed. If the biological unit is an RNA unit, the DNA is then transcribed to

the corresponding RNA. The resultant is then screened for interaction with a ligand that interacts with a discontinuous epitope of the single biological unit. Those that are identified with such positive interaction are then produced and can serve to simulate the native discontinuous epitope.

The interview between Examiner Forman and the undersigned attorney on February 19, 2003, is hereby gratefully acknowledged. In this interview, the examiner stated that the single biological unit appeared to read on a genome and, therefore, to encompass the shuffling of Huse and others in the art. In response, it was pointed out that the claims are drawn to a single biological unit and not the variety of antibodies of Huse and others, and, as such, the instantly claimed method is not taught by the prior art. The amendments to the claims presented herewith were discussed at the interview. The examiner agreed that the suggested amendments appeared to overcome the teaching of Huse, which produces a variety of antibodies.

The examiner has reconsidered the restriction requirement and made it final. As to applicants' argument that Marks does not disclose the special technical feature shared by all the claims of the present application, the examiner stated that Marks still discloses the technical feature that links Groups I-V. The examiner states that Marks specifically teaches randomly ligating at least two DNA

fragments, citing Figure 1, lines 11 to the end. This discussion of random assembly refers to Reference 69, which is the Huse et al reference of record in this case. Thus, Huse and Marks teach the same thing. In her discussion of Huse, the examiner states, in the last paragraph of page 16 of this action, that the present claims do not exclude the presence of ligated fragments from a plurality of biological units as is done in Huse because the open claim language "comprising" in claim 159 encompasses additional biological units. As will be discussed below, the present claims have now been amended to provide that the plurality of DNA fragments consist of fragments that appear in a DNA sequence that encodes the single biological unit and that the library which is created consists of oligonucleotides from said plurality of DNA fragments, said fragments being randomly ligated. Accordingly, in light of this modified claim language, which ensures that the claims do not read on a library made out of fragments from a plurality of different biological units, it is urged that no reading of the present claims can read on the procedure of Marks, which is really the procedure of Huse. Thus, for the same reasons as will be discussed hereinbelow with respect to the anticipation rejection, there is no reference that discloses the special technical feature found by all of the claims of the present application. Reconsideration and withdrawal of this unity of rejection requirement and examination of all of the claims now present in the case are, therefore, respectfully urged.

Claims 144-146, 149-151, 155, 156, 159-161, 163-165, 169 and 170 have been rejected under 35 U.S.C. §102(b) as being anticipated by Huse. The examiner states that given the broadest reasonable interpretation of the claim, the claim to a single biological unit encompasses the antibody of Huse and, therefore, Huse discloses the method as claimed. In her response to applicants' arguments at page 16 of the official action, the examiner states that applicants' argument that the library of Huse contains a lot more than ligated fragments from a single biological unit because it contains ligated fragments from an entire library of biological units is unpersuasive because the open claim language "comprising" encompasses additional biological units. The examiner states that the claim does not exclude other DNA fragments that encode other biological units. Further, the examiner states that the claims recite "randomly ligated", which does not limit the order or arrangement of the ligated fragments. This rejection is respectfully traversed.

The present amendment tightens the claims in order to close the loophole noted by the examiner by which the present claims could be interpreted more broadly than had been originally intended. As amended, the present claims leave the word "comprising" in the preamble so as not to exclude the possibility of additional steps in the method. However, the definition of the plurality of DNA fragments and the definition of library has been clarified to state that there is provided "a plurality of DNA fragments consisting of

fragments, each of which appears in a DNA sequence that encodes the single biological unit". Furthermore, the second step reads that there is created "a library consisting of oligonucleotides from said plurality of DNA fragments". Thus, the "plurality of DNA fragments" can only include fragments that appear in a single biological unit and exclude fragments that are a part of other biological units. Furthermore, the amendment of paragraph of (b) specifies that the library consists of oligonucleotides, which oligonucleotides are created from said plurality of DNA fragments. Thus, the definition of library excludes the presence of oligonucleotides that do not have at least two fragments that appear in the single biological unit. The library of Huse has oligonucleotides with fragments from millions of biological units, i.e., millions of antibodies. The random ligation of Huse does not create a library full of oligonucleotides, each containing at least two fragments which appear in a single biological unit. Within Huse's library, Huse only produces one oligonucleotide containing at least two fragments from a single biological unit. One does not a library make.

Claims 144 and 159 have also been amended to define "single biological unit" as consisting of a protein or consisting of two or more proteins which interact to form a complex (see previously-appearing claims 155, 156, 169 and 170). The addition of this definition makes clear that the single biological unit cannot be an entire genome. In the course of the interview, the examiner expressed the concern

that the term "antibody" could broadly be considered as a single biological unit to the extent that the term generically covers different variable units. However, it is urged that one of ordinary skill in the art, reading the present specification as a whole, would not consider that a "single biological unit" could encompass the entire library of possible variable units of an antibody. A single biological unit must be a specific protein or a group of specific proteins that form a complex. Thus, it is inappropriate to read Huse's library of fragments, from the entire universe of millions of antibodies, to consist of fragments of DNA that encode a single biological unit. Each specific antibody is a single biological unit. The present claims do not read on fragments of a plurality of biological units, which is what the library of Huse is. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 147, 148, 154, 162 and 168 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Huse in view of Stemmer. The examiner states that Stemmer teaches mechanical cutting of DNA, as well as synthesis of DNA, eukaryotic expression systems, etc. This rejection is respectfully traversed.

Stemmer does not fulfill any of the deficiencies of Huse discussed above with respect to the independent claims. Thus, regardless of the applicability of Stemmer to the dependent claims discussed, the claims are allowable for the same reasons as discussed hereinabove with respect to the

independent claims from which they depend. Reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

Claims 152, 153, 166 and 167 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Huse in view of Marks. This rejection is respectfully traversed.

Marks is a review that discusses the technique of Huse, as well as similar techniques. However, as discussed above, the present claims do not read on making a repertoire of antibodies on phage. Thus, Marks does not fulfill any of the deficiencies of Huse with respect to the independent claims as discussed hereinabove. Regardless of the obviousness of the various features of the dependent claims, these claims are allowable for the same reasons as discussed hereinabove with respect to the independent claims from which they depend. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 177 and 179 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Huse in view of Stemmer. The examiner states that it would have been obvious to one of ordinary skill in the art to modify the fragments of Huse "using routine experimentation and to derive fragments (e.g., of about 50 to about 150) for the obvious benefits of optimizing fragment length to thereby maximize identification and production of desired peptides." This rejection is respectfully traversed.

Huse is not involved with identification and production of desired peptides. It is only interested in generating a large combinatorial library of the immunoglobulin repertoire. Thus, Huse provides no motivation to use small fragments. Indeed, Huse requires the entire antibody heavy and/or light chain, or at least the variable regions of the entire chain, all of which are larger than about 150 base pairs. Thus, no combination of Stemmer with Huse would make obvious the modification of Huse to use such smaller antibody fragments. This is not a matter of optimization and is, in fact, taught away from by Huse. Furthermore, claims 177 and 179 are allowable for the same reasons as the claims from which they depend as discussed hereinabove. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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